

Remarks

Claims 22-25, 32-34, 38-46, 48 and 49 are pending in the subject application. Claim 46 has been amended to change its dependency and claim 49 has been amended to correct the preamble. Accordingly, claims 22-25, 32-34, 38-46, 48 and 49 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the objection of claim 41.

Claims 22-25, 32-34, and 38-46 are rejected under 35 U.S.C. § 103(a) as obvious over Boschetti (2002) in view of Xiang *et al.* (2001) and Burton *et al.* (1998). Applicants respectfully traverse and request reconsideration because the references, taken either alone or in combination, do not teach or suggest every claim element.

As the Patent Office is aware, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1741 (2007). Rather, each of three basic criteria must be met in order to establish a *prima facie* case of obviousness. First, there must be an apparent reason for some teaching, suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *See KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. at 1941. In addition, there must be a reasonable expectation of success. (The *KSR* Court held that "a simple arrangement of old elements with each performing the same function it had been known to perform" must further yield no more than one would expect from such an arrangement.) *Id.* at 1941. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. *In re Royka*, 490 F.2d 981, 985 (C.C.P.A. 1974).

The present invention provides a novel and advantageous process for the purification of interleukin-18 binding protein (IL-18BP). The claims require, among other things, the steps of loading IL-18BP-containing fluid onto a hydrophobic charge-induction chromatography (HCIC) resin equilibrated to a pH of  $6.1 \pm 0.1$  with a buffer and eluting the IL-18BP from said hydrophobic charge-induction chromatography resin with a buffer having a pH of  $8.4 \pm 0.1$ . Unexpectedly, absorption at  $6.1 \pm 0.1$  followed by elution at  $8.4 \pm 0.1$  yields IL-18BP with a high purity of 98%

(Table VIII). As a result, the present invention successfully solves a need in the art for the purification of IL-18BP (specification at page 5, lines 30-31).

The Boschetti reference is directed to the use of HCIC for purification of antibodies such as IgG and IgA (Boschetti Abstract at page 333, right column, 3<sup>rd</sup> paragraph, stating that “hydrophobic charge-induction chromatography (HCIC), described here, represents an improvement towards achieving the ideal situation in the design of an antibody-selective absorbent”). Specifically, HCIC is based on the pH-dependent behavior of dual model ionizable hydrophobic ligands. The process involves absorption followed by subsequent desorption of the protein, and is controlled on the basis of pH rather than salt concentration (Boschetti at page 333, right column, 4<sup>th</sup> paragraph). Desorption occurs when the pH is lowered (Boschetti Abstract and page 333, right column, 4<sup>th</sup> paragraph). Specifically, antibody absorption occurs at a pH of 8.5 and desorption occurs at a pH of 4.0 (see legend to Fig. 2 and the paragraph bridging pages 333-334).

Applicants respectfully submit that Boschetti fail to teach or suggest the presently claimed IL-18BP purification process for the following reasons. First, the reference simply relates to the purification of antibodies. It does not teach or suggest successful purification of any other protein. The HCIC purification process is based on the pH-dependent, hydrophobic / electrostatic interactions between the protein and the ligand. There is no correlation between the hydrophobic / electrostatic characteristics of antibodies and any other proteins such as IL-18BP. Nothing teaches or suggests whether the antibody-selective pH conditions in Boschetti, or how to modify these conditions, would lead to the absorption and subsequent desorption of IL-18BP, which are based on hydrophobic / electrostatic interactions between IL-18BP and the ligands, with an anticipated success.

The lack of teaching or suggestion in Boschetti toward the IL-18BP purification process is further evidenced by the contrasting pH conditions between the reference teachings and that of the present invention. In Boschetti, absorption is performed at a pH of 8.5, followed by desorption at a pH of 4.0. In comparison, in the present invention, absorption is performed at a pH of  $6.1 \pm 0.1$ , followed by desorption at a pH of  $8.4 \pm 0.1$ , conditions that are the opposite of those taught in Boschetti.

Recognizing the significant deficiencies in the teachings of Boschetti, the Office Action seeks to remedy these issues by reliance on Burton *et al.* and Xiang *et al.* The Office Action asserts at

page 4 that “Xiang *et al.* teach that approximately 60% of the mature human IL-18BP **resembles an immunoglobulin (Ig) domain** that includes a highly conserved pair of cysteines and tryptophan residues and that IL-18BP was purified from a cell culture supernatant” (emphasis added). Burton *et al.* is relied upon for the assertion that proteins can be purified using hydrophobic charge induction chromatography and that elution conditions for the purification of proteins can range between a pH of 5 and 9 (Office Action at page 4).

At page 5 of the Office Action, it is argued that “[u]nder KSR, it’s now apparent “obvious to try may be a more appropriate test in more situations” than previously contemplated. Thus, the Office Action argues that with the combined teachings of Boschetti, Xiang *et al.*, Burton *et al.* and the general knowledge of skill in the art, it would have been obvious for one skilled in the art to specifically develop a process for the purification of IL-18BP. The Office Action further argues that it would have been obvious to modify the process of Boschetti and Xiang *et al.* because “a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense” (Office Action, paragraph bridging pages 5-6).

With regards to the “obvious to try” argument at pages 5-6, the Supreme Court in *KSR* has warned against the temptation of improper hindsight reconstruction, and reiterated that “it can be important to identify a reason that would have prompted a person of ordinary skilled in the relevant field to combined the elements in the way the claimed new invention does.” *KSR International Co. v. Teleflex, Inc.* at 1741. The Court in *KSR* held that a finding of obviousness requires the prior art to provide “a finite number of identified, predictable solutions.” *KSR International Co. v. Teleflex, Inc.* at 1742. The number of options must be “small or easily traversed,” a person of ordinary skill must have a good reason to pursue the known options, and the combination of familiar elements according to known methods must yield no more than predictable results. *KSR International Co. v. Teleflex Inc.* at 1742, *Bayer Schering Pharma AG. v. Barr Lab., Inc.*, 91 USPQ2d 1565, 1572-73 (Fed. Cir. 2009). Thus, “an invention would not have been obvious to try when the inventor would have to try all possibilities in a field unreduced by direction of the prior art, . . . where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices

is likely to be successful.” *Bayer Schering Pharma AG. v. Barr Lab., Inc.*, 91 U.S.P.Q.2d at 1572-73, *In re O’Farrell*, 853 F.2d 894 (Fed. Cir. 1988).

The Office Action asserts at pages 6-7 that “however, the issue regarding desorption of proteins is not relevant to claim 22, since the conditions recited in the two references are specific to an antibody and chymosin that have distinct purification requirements from ones needed for the purification of IL-18BP.” Applicants respectfully disagree. In the evaluation of *prima facie* obviousness, M.P.E.P. 2142 states that “the examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness.” *In re Oetiker*, 977 F. 2d 1443, 1445 (Fed. Cir. 1992). To support the conclusion that the claimed invention is directed to obvious subject matter, either references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. *Ex parte Clapp*, 227 U.S.P.Q. 972, 973 (Bd. Pat. App. & Inter. 1985).

In this case, Applicants submit that the claimed invention is not obvious on the grounds articulated in the Office Action. Applicants submit that the combination of Boschetti, Xiang *et al.* and Burton *et al.* would not have lead one skilled in the art to the claimed processes. Particularly, while Burton *et al.* indicates that adsorption and elution of proteins can be performed between a pH of 5-9, one skilled in the art would not have loaded IL-18BP at an acidic pH ( $6.1 \pm 0.1$ ) and eluted IL-18BP at a basic pH ( $8.4 \pm 0.1$ ) in view of the cited references. The Office Action has argued that “Xiang *et al.* teach that approximately 60% of the mature human IL-18BP resembles an immunoglobulin (Ig) domain that includes a highly conserved pair of cysteines and tryptophan residues” in support of its position that one skilled in the art would expect to be able to purify IL-18BP using hydrophobic charge induction chromatography resins. Yet, no scientific reasoning or supporting evidence is provided in the Office Action establishing why one skilled in the art would have any expectation that, given the resemblance of IL-18BP to immunoglobulin molecules, one could or would elute IL-18BP from hydrophobic charge induction chromatography resins under conditions that are completely opposite of those suitable for purification of immunoglobulin molecules. Rather, the cited combination of references would have led one skilled in the art to have

loaded IL-18BP onto hydrophobic charge induction under basic conditions and eluted under acidic conditions because of the high degree of similarity between IL-18BP and immunoglobulin molecules.

With regards to the “routine optimization” argument at page 7, Applicants respectfully note that “where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges,” where improvement is achieved only by routine experimentation, and where the only difference between the claim and the prior art is merely a difference in degree such as a few percentage points, not a difference of kind. *In re Aller*, 220 F.2d 454, 455-57 (C.C.P.A. 1955). In this case, the differences between the claimed invention and the cited prior art are differences of a kind, namely loading under acidic conditions and eluting under basic conditions whereas the cited prior art teaches loading under basic conditions and elution under acidic conditions. Thus, it cannot be said that the claimed elution conditions are merely “routine optimization”. Accordingly, Applicants respectfully assert that the claimed invention is not obvious over the cited reference, and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

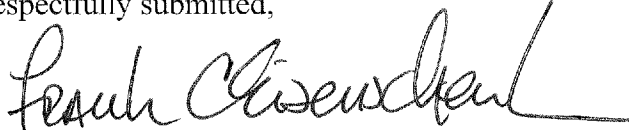
It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants’ agreement with or acquiescence in the Examiner’s position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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